REMARKS/ARGUMENTS

Claims 1-12 and 14-20 have been rejected. Applicants have not cancelled, added, or amended any claims. Accordingly, claims 1-12 and 14-20 are pending in the application. Reconsideration of the claims is respectfully requested in view of the following remarks. The Examiner's comments in the Office Action are addressed below in the order set forth therein.

The Rejections of the Claims Under 35 U.S.C. §103(a) Should Be Withdrawn

Claims 1-12 and 15-20 are rejected under 35 U.S.C. §103(a) as being obvious in light of Roof *et al.* (1997) *Molecular and Chem. Neuropathology 31*:1-11, in view of Backstrom *et al.* (U.S. Patent No. 6,455,516) and Gee *et al.* (RE 35,517). Claims 1-12 and 15-20 are also rejected as being obvious in light of the references cited above, further in view of Roof *et al.* (1992) *Restoration of Neurology and Neuroscience 4*:425-427. Because of the similarities of these rejections, they will be addressed together. These rejections are traversed for the reasons provided below.

The present claims are directed to either a method for treating a traumatic central nervous system injury or a method of decreasing neurodegeneration following a traumatic injury to the central nervous system. Both methods comprise the steps of identifying a patient with a traumatic central nervous system injury and administering to that patient a pharmaceutical composition comprising allopregnanolone. Applicants submit that the combination of references cited above does not render Applicants' claimed invention obvious.

To establish a *prima facie* case of obviousness there must be, among other things: 1) some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or combine the reference teachings; and 2) there must be a reasonable expectation of success. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). Applicant respectfully submits that when establishing a *prima facie* case of obviousness, one must consider the teachings of the cited reference(s) as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*,

469 U.S. 851 (1984). For the reasons provided below, it is Applicant's contention that one of skill in the art would not have been motivated to combine the references cited by the Examiner, nor would they have had a reasonable expectation of success.

The Roof *et al.* (1997) reference teaches administration of progesterone to rats following a medial frontal cortex contusion. The Roof *et al.* (1992) reference teaches that the administration of progesterone to rats following a medial frontal cortex contusion reduces brain edema. The Gee *et al.* reference discloses methods of modulating brain excitability through the administration of progesterone metabolites such as allopregnanolone to patients suffering from stress, anxiety, and seizure activity. The Backstrom *et al.* reference teaches the use of epiallopregnanolone (3β-hydroxy-5α-pregnan-20-one) for the treatment of steroid-induced central nervous system (CNS) disorders. While the Examiner acknowledges that neither of the Roof *et al.* references explicitly teach the administration of the progesterone metabolite allopregnanolone within the presently claimed methods (See Office Action dated August 24, 2006, pages 4 and 6), the Examiner goes on to state that in light of Backstrom *et al.* and Gee *et al.*, one of skill in the art would have been motivated to administer allopregnanolone within the claimed methods with a reasonable expectation of success. Applicants disagree.

First, Applicants submit that one of skill in the art would not have been motivated to combine the teachings of the references cited by the Examiner. The motivation on which the Examiner relies to combine the cited references is based upon inaccurate interpretations of both the Backstrom *et al.* and Gee *et al.* references. With respect to Backstrom *et al.*, the Examiner states that this reference teaches that allopregnanolone is a progesterone metabolite that is useful for treating CNS disorders. In fact, Backstrom *et al.* teach the use of epiallopregnanolone (3β-hydroxy-5α-pregnan-20-one) for the treatment of steroid-induced CNS disorders, including disorders caused by allopregnanolone (3α-hydroxy-5α-pregnan-20-one) (*See, e.g.*, Backstrom *et al.* column 1, lines 14-23 and column 3, lines 20-29). In other words, the Backstrom *et al.* reference actually teaches away from its combination with the other cited references. Backstrom *et al.* teach that allopregnanolone is a sedative compound that can cause disorders such as epilepsy, depression, and stress; the same disorders for which Gee *et al.* teach the administration of allopregnanolone as a treatment (*See, e.g.*, Backstrom *et al.* column 3, lines 20-29, column 6,

lines 21-31, and claims 1 and 4). It is improper to combine references where the references teach away from their combination. *In re Grasselli*, 713 F.2d 731, 218 USPQ 769 (Fed. Cir. 1983). Accordingly, based on the Backstrom *et al.* reference, one of skill in the art would not have been motivated to combine the cited reference teachings.

With respect to Gee *et al.*, the Examiner states on pages 4 and 6 of the Office Action dated August 24, 2006 that "Gee et al. discloses that progesterone metabolites including ... allopregnanolone, are useful in a method for treating seizure disorders ... Gee et al. also discloses that the beneficial effect of progesterone is related to the conversion of progesterone to the active metabolites including allopregnanolone since the metabolites and derivatives possess higher potency and efficacy than progesterone" (emphasis in original). However, Gee *et al.* does not teach or suggest that allopregnanolone would have higher potency and efficacy in the treatment of different disease states such as in patients following a traumatic injury to the CNS as instantly claimed. As outlined in part 4(a) of the declaration by Dr. David Wright filed under § 1.312 on December 19, 2003:

> Gee *et al.* teach that both progesterone and many of its metabolites bind with high affinity to a unique GABA/GBR complex and that these metabolites delay onset of myoclonus following TBPS induced seizures in mice. There is no data demonstrating that progesterone and allopregnanolone are effective at treating other disease states, such as traumatic brain injury, and certainly no teaching that *all* of progesterone's beneficial effects are related to progesterone's conversion into its various metabolites.

Accordingly, based on the Gee *et al.* reference, one of skill in the art would not have been motivated to combine the cited reference teachings.

In addition to the lack of motivation to combine the teachings of the references cited by the Examiner, Applicants submit that the cited references would not have provided one of skill in the art with a reasonable expectation of success with respect to the administration of allopregnanolone within the presently claimed methods. The mechanism of action by which progesterone and allopregnanolone mediate their effects to treat patients identified as having a traumatic central nervous system injury is unknown and one of skill would not assume progesterone and allopregnanolone have identical mechanisms of action for any and all disorders

that affect the central nervous system. As outlined in the declaration by Dr. Wright cited above, the assumption that compounds with similar precursors or structure have identical mechanisms of action is flawed and incompatible with known scientific data (See part 4(c) of the declaration of Dr. Wright filed on December 19, 2003). This is particularly so in the case of progesterone metabolites, since various progesterone metabolites have been found to exhibit divergent and conflicting mechanisms of action compared to progesterone and to each other (See parts 4(c)(i)-(iv) of the declaration of Dr. Wright filed on December 19, 2003). Accordingly, one of skill in the art would not have had a reasonable expectation of success in the substitution of allopregnanolone for progesterone in the methods of Roof *et al.* based on the findings of Gee *et al.* relating to seizure disorders or the teachings of Backstrom *et al.* that allopregnanlone causes steroid-induced CNS disorders.

The Backstrom *et al.* reference provides further evidence that the cited references would not have provided one of skill in the art with a reasonable expectation of success with respect to the administration of allopregnanolone within the presently claimed methods. The Backstrom *et al.* reference presents experimental evidence showing that different progesterone metabolites exhibit divergent and conflicting mechanisms of action. For example, with respect to the four progesterone metabolites allopregnanolone (3α-hydroxy-5α-pregnan-20-one), pregnanolone (3α-hydroxy-5β-pregnan-20-one), epiallopregnanolone (3β-hydroxy-5α-pregnan-20-one), and epipregnanolone (3β-hydroxy-5β-pregnan-20-one), allopregnanolone and pregnanolone were shown to inhibit synaptic signal transmission in CA1 hippocampal neurons in an *in vitro* hippocampal slice model, while epiallopregnanolone blocked this effect and epipregnanolone did not (See Backstrom *et al.*, column 7, lines 16 to 47). Furthermore, in an *in vivo* rat model, epiallopregnanolone was shown to block the sedative effects of allopregnanolone and pregnanolone (See Backstrom *et al.*, column 8, line 13 to column 9, line 26). Clearly, one of skill in the art cannot predict with any reasonable expectation of success that a progesterone metabolite shown to exhibit certain effects in one model system or disorder will exhibit the same effects in another distinctly different model system or disorder. Accordingly, one of skill in the art would not have had a reasonable expectation of success in the substitution of allopregnanolone for progesterone in the methods of Roof *et al.* on the basis of the findings of

Gee *et al.* relating to seizure disorders, particularly in light of the teachings of the Backstrom *et al.* reference.

In addition to the lack of motivation to combine the teachings of the references cited by the Examiner and the lack of a reasonable expectation of success, Applicants also maintain that this obviousness rejection amounts to hindsight reconstruction of the claimed invention. None of the cited references would guide one of skill in the art to select allopregnanolone from among the multitude of progesterone metabolites and administer this compound to a patient identified as having a traumatic central nervous system injury. Only through hindsight and with knowledge of the present application would one select references at random that mention various aspects of the claimed invention. This is an improper standard. "One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." *In re Fine*, 837 F.2d 1071, 1075, 5 USPQ 2d 1596, 1600 (Fed. Cir. 1988); see also *In re Fritch*, 23 USPQ2d 1780, 1784 (Fed. Cir. 1992) (ruling that it is impermissible to use the claimed invention as an instruction manual or template to piece together the teachings of the prior art to render it obvious).

In summary, one of skill in the art would not have been motivated to combine the references cited by the Examiner, nor would they have had a reasonable expectation of success. In addition, the Examiner uses impermissible hindsight reconstruction in the selection of references that form the basis of this rejection. Accordingly, a *prima facie* case of obviousness has not been established and this rejection under 35 U.S.C. §103(a) should be withdrawn.

Claim 14 is rejected under 35 U.S.C. §103(a) as being obvious in light of the primary references cited above, further in view of Weinshenker *et al.* (U.S. Patent No. 5,068,226). This rejection is traversed for the reasons provided below.

The shortcomings of the primary references in failing to render Applicants' claimed invention obvious have been described above. The Examiner cites the Weinshenker *et al.* reference for teaching that cyclodextrins are useful as carriers for improving the delivery of active agents such as certain steroids. However, the Weinshenker *et al.* reference fails to provide either a motivation to combine or modify the teachings of the primary references to arrive at the

present claims, or a reasonable expectation of success in carrying out the methods of the present claims. Because the Weinshenker *et al.* reference fails to remedy the shortcomings of the Roof *et al.* (1997), Roof *et al.* (1992), Backstrom *et al.*, Gee *et al.* and references, a *prima facie* case of obviousness has not been established and this rejection under 35 U.S.C. §103(a) should be withdrawn.

CONCLUSION

In view of the aforementioned remarks, Applicants submit that the rejections of the claims under 35 U.S.C. §103(a) are overcome. Accordingly, Applicants submit that this application is now in condition for allowance. Early notice to this effect is solicited.

If in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject Application, the Examiner is invited to call the undersigned.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

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